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Opposite effects of L-dopa and DBS-STN on saccadic eye movements in advanced Parkinson's disease☆

Małgorzata Dec-Ćwiek[a,*], Marcin Tutaj[a], Jean-Michel Gracies[b], Jens Volkmann[c], Monika Rudzińska[d], Agnieszka Słowik[a,1], Andrzej Szczudlik[a,1]

[a] Department of Neurology, Jagiellonian University, Medical College, Kraków, Poland
[b] Department of Neurorehabilitation, EA BIOTN, Henri Mondor Hospital, Créteil, France
[c] Department of Neurology, Julius-Maximilians-University Würzburg, Würzburg, Germany
[d] Department of Neurology, Medical University of Silesia, Faculty of Medicine, Katowice, Poland

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ABSTRACT

Objective: To assess the effects of L-dopa and deep brain stimulation of the subthalamic nucleus (DBS-STN) on saccadic eye movements in patients with Parkinson's disease (PD).
Methods: Visually and internally guided horizontal saccades were evaluated using a saccadometer in 64 patients with advanced PD and 48 healthy controls. Forty-four pharmacologically treated patients were assessed in their "med-off" (OFF) and "med-on" (ON) status, whereas 20 DBS-STN treated patients were assessed in their "med-off, stim-off" (OFF) and "med-off, stim-on" (ON) status.
Results: In all PD patients the saccades in the OFF status were delayed, slower and smaller ($p < 0.01$) than in controls. In pharmacologically treated patients all studied parameters showed tendency to worsen in the ON status as compared to the OFF status. In contrast, activating DBS-STN showed tendency to improve all studied parameters. Comparison of the studied saccade parameters between the ON status of DBS-STN treated patients, ON status of the pharmacologically treated patients and the controls showed that 73% of these parameters in the DBS-STN treated patients were similar as in the controls. While in the pharmacologically treated patients only 26% of these parameters were similar as in the controls.
Conclusion: This prospective study comparing the influence of L-dopa and DBS-STN on saccades in advanced PD showed contrasting results between these two treatments; the majority of the studied parameters in patients on DBS-STN were similar as in the controls.

☆ Statistical analysis conducted by Romuald Polczyk, PhD, Institute of Physiology, Jagiellonian University, Kraków, Poland.
* *Corresponding author at*: Department of Neurology, Jagiellonian University, Medical College, Botaniczna 3 Str., 31-503 Kraków, Poland. Tel.: +48 12 424 86 00; fax: +48 12 424 86 26.
E-mail address: malgorzatadec@yahoo.co.uk (M. Dec-Ćwiek).
[1] These authors contributed equally to the manuscript.
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1. Introduction

There have been several reports describing abnormalities of eye movements in Parkinson's disease (PD), such as difficulties in stabilizing the image on the retina, or difficulties in redirecting the line of sight to a new object (visually or internally guided saccades). Both difficulties can be affected either by the disease itself or by treatment [1].

Saccades are more easily quantified and less dependent on biomechanical parameters than limb movements, thus, they might be a more appropriate for studying movement control in PD. In this disease, measurements of repetitive saccadic movements, in contrast to measurements of limb movements, can be easily performed even in OFF status [2,3]. Saccadic abnormalities in PD essentially resemble somatomotor symptoms, being characterized by increased reaction time, decreased amplitude and decreased velocity, and consequently may reflect hypometria and bradykinesia [4].

Previous studies on the effects of deep brain stimulation of the subthalamic nucleus (DBS-STN) or L-dopa on saccades have led to varying results and their clinical significance was not clear [2,5–8]. We compared the influence of L-dopa and DBS-STN on saccades in patients with advanced PD, using a prospective protocol.

2. Material and methods

2.1. Study participants

The participants were recruited from the Movement Disorders outpatient clinic of the Department of Neurology. Forty-four of the study patients had advanced PD treated only with L-dopa (Hoehn and Yahr scale off drug, 4.1 ± 0.2) and 20 were additionally treated with bilateral DBS-STN, all implanted using the same surgical protocol (mean follow-up since DBS-STN procedure, 2 years; H&Y off drug, 4.0 ± 0.2) [8,9]. Exclusion criteria were as follows: cognitive dysfunction (<24 points on the Mini-Mental State Examination, MMSE), moderate-to-severe depression (>16 points on the Hamilton Rating Scale for Depression, HRSD) [10], color blindness (score <0.1 at the best corrected visual performance, using a standard Snellen Chart), red color vision impairment using the Ishihara Color Test, and severe eye-movement impairments upon neurological examination.

Forty-eight healthy subjects matched by age and gender (28 males; mean age 60 ± 8) served as controls.

All participants provided written, informed consent. Ethical approval was given by the institutional review board.

2.2. Study design

Social and demographic characteristics, medical history including age at disease onset and course of disease as well as L-dopa equivalent daily dose (LEDD) were recorded from all participants during the initial visit and neurological examination was performed, including visual acuity, color distinction and eye movement assessment. Additionally, study subjects were rated on MDS-UPDRS part III in their best clinical ON state–after intake of 1.5 times the equivalent of their morning medication dose – and filled out the quality of life PDQ-39 questionnaire. PD was staged according to the Hoehn-Yahr scale (H&Y) [8], and PD subtype (tremor-dominant vs. bradykinesia, postural instability and gait difficulty, PIGD) [11] was identified in each patient.

During the study period, PD subjects were examined twice, in their clinically defined L-dopa-OFF and ON status, on 2 consecutive days. Following classical guidelines, the first assessment of pharmacologically treated patients was performed in the clinically defined OFF-status after drug withdrawal for at least 12 h for L-dopa and 48 h for other antiparkinsonian drugs (''med off'') [12,13]. The second assessment was carried out approximately 45–60 min after L-dopa intake (1.5 times the equivalent of morning medication dose) in the best ON status (defined as the status when patient and examiner agreed that the patient's best ON was attained) [14]. The assessment of the DBS-STN patients was performed in the clinically defined OFF-status as in the previous group (''med off''), with the stimulator switched on (''stim on'') and repeated 30 min after switching the neurostimulator off, in the stimulation OFF state (''med off'' and ''stim off'') [12,13]. The assessment of patients in their ON (pharmacologically treated patients: ''med on''; DBS-STN patients: ''med off'' and ''stim on'') and OFF states (pharmacologically treated patients: ''med off''; DBS-STN patients: ''med off'' and ''stim off'') involved both neurological examination (including MDS-UPDRS part III assessment) and saccadic eye-movement recording.

In control subjects, only one saccadic eye-movement recording was performed.

2.3. Saccade assessment

The participants were seated in a comfortable armchair, one meter away from a board with light-emitting diodes along a horizontal line. Saccadic eye movements were recorded using a miniaturized infra-red 1 kHz saccadometer, low pass filtered at 250 Hz with 12 bit resolution (Ober Consulting, Poznan, Poland) [15]. While the device was mounted on the subject's forehead, resting on the bridge of the nose, five built-in low-power lasers projected red 13 cd m^{-2} spots subtending some 0.1 degrees in horizontal line in the midline at ±20 degrees from central vision. As stimuli moved exactly with the head, no head-restraint was necessary, unless desired by the patient.

Participants underwent 3 experimental runs in a random order. Saccades were determined to begin when eye velocity was greater than 20°/s. Of all performed saccades, only centrifugal visually and internally guided saccades were analyzed. Each experimental run was preceded by a number of preliminary saccades (usually 10, toward a 10-deg or 20-deg lateral target that appeared randomly right or left), used to calibrate the device. Each experimental run lasted 10–15 min and participants rested between trials to minimize fatigue.

For visually guided saccades, a test with a gap paradigm was performed. Participants were instructed to initially fixate a central fixation point illuminated for 3.5 s, then to make a saccade toward a 10-deg or 20-deg lateral target that appeared randomly right or left 200 ms (temporal gap) after the disappearance of the fixation point [5]. Participants were cued

Table 1 – Demographic and clinical characteristics of PD patients.

Parameter	DBS-STN treated patients $n = 20$	Pharmacologically treated patients $n = 44$	p
Male/female ratio	6/14	20/24	n.s.
Age (years)	63	65	n.s.
(mean ± SD)	(±7)	(±10)	
Disease duration (years)	11.9	10.77	n.s.
(mean ± SD)	(±5.42)	(±3.85)	
PIGD (%)	85%	68.18%	n.s.
LEDD [mg]	454	1061.14	0.0001
(mean ± SD)	(±334.99)	(±326.65)	
MDS-UPDRS III (OFF status)	34.15	47.47	<0.00001
(mean ± SD)	(±7.17)	(±10.09)	
PDQ-39	44.85	68.16	0.0016
(mean ± SD)	(±26.61)	(±23.05)	

n.s., not significant; PIGD, postural instability and gait difficulty subtype of the disease; LEDD, L-dopa equivalent daily dose; MDS-UPDRS III, Unified Parkinson's Disease Rating Scale. Part III (OFF status for DBS-STN treated patients means ''med-off and stim-off'' and for pharmacologically treated patients means ''med-off''); PDQ-39, the Parkinson's disease questionnaire.

Table 2 – Saccadic parameters in PD patients in the OFF status and controls.

Visually guided saccades	DBS-STN treated patients $n = 20$ (A)	Pharmacologically treated patients $n = 44$ (B)	Controls $n = 48$ (C)	p
Latency [ms]	325.7	256.8	229.8	(A–C) < 0.01
	(±116.2)	(±68.5)	(±38.5)	
Amplitude 10°	7.6	8.9	9.7	(A–C) < 0.01
	(±2.5)	(±2.3)	(±1.9)	
Amplitude 20°	12.6	15.3	17.9	(A–C) < 0.01
	(±4.3)	(±4.1)	(±4.1)	(B–C) < 0.01
Peak velocity 10° [°/s]	224.2	303.3	312.1	(A–C) < 0.01
	(±66.6)	(±105.0)	(±73.4)	(A,B) < 0.01
Peak velocity 20° [°/s]	262.7	360.9	381.0	(A–C) < 0.01
	(±81.6)	(±118.0)	(±94.0)	(A,B) < 0.01
Antisaccades				
[*n*]	34	38	61	(A–C) < 0.01
				(B–C) < 0.01
Latency [ms]	520.9	515.9	324.9	(A–C) < 0.01
	(±130.4)	(±247.2)	(±61.6)	(B–C) < 0.01
Peak velocity [°/s]	202.2	240.9	291.8	(A–C) < 0.01
	(±53.1)	(±85.2)	(±87.0)	(B–C) = 0.03
Memory-guided saccades				
[*n*]	25	22	47	(A–C) = 0.02
				(B–C) < 0.01
Latency 10° [ms]	652.1	571.0	408.5	(A–C) = 0.01
	(±331.1)	(±307.5)	(±200.0)	(B–C) = 0.03
Latency 20° [ms]	521.4	566.7	410.4	(B–C) = 0.01
	(±225.6)	(±215.2)	(±179.6)	
Amplitude 10°	8.8	10.2	11.3	(A–C) < 0.01
	(±2.0)	(±3.9)	(±3.4)	
Amplitude 20°	16.7	16.0	20.5	(B–C) < 0.01
	(±1.8)	(±5.8)	(±6.3)	
Peak velocity 10° [°/s]	199.1	241.9	284.4	(A–C) = 0.01
	(±45.5)	(±125.5)	(±96.0)	(B–C) = 0.02
Peak velocity 20° [°/s]	215.7	288.0	356.8	(A–C) < 0.01
	(±95.6)	(±130.1)	(±114.4)	(B–C) < 0.01

Data are mean (±SD).
$p < 0.05$.
n, number of saccades properly accomplished (%).

to make 40 saccades in each direction in a random order (80 saccades total) and latency, amplitude, as well as peak saccadic velocity were evaluated. The following visually guided parameters were studied: amplitudes for 10 or 20 degree-saccades, latency and peak saccadic velocity for 10 or 20 degrees.

The internally guided saccades were tested using antisaccadic and memory-guided tests for which subjects were tested for 60 trials, 30 saccades in each direction in a random order.

For the antisaccadic test, the same stimulus condition as in the visually guided saccade test was used, but participants were instructed that after the appearance of the eccentric target (10-deg or 20-deg), they were to generate a saccade away from it to its mirror location [5].

For the memory-guided test, participants were instructed to initially fixate the central fixation point illuminated for 4.5 s. A 50 ms flash then appeared, randomly right or left with unpredictable eccentricity (10-deg or 20-deg). After the flash, the central fixation point remained illuminated for 7 s, and participants were supposed to keep their eyes on the central fixation point during the entire delay. Participants were required to move their eyes toward the memorized location of the flash as soon as the central fixation point was switched off. Two seconds later, a target with the same location as the flash was illuminated to allow the corrective saccade to be executed, if needed [5]. The percentage, latency, amplitude (memory-guided saccades) and peak saccadic velocity of properly accomplished internally-guided saccades were evaluated.

2.4. Statistics

Due to violated normality assumption in the data distributions, all parameters were logarithmically transformed. Descriptive statistics provided means, standard deviations and standard errors for all variables. Hypotheses concerning the differences between ON and OFF were tested by means of a two-factor analysis of variance with one repeated-measures factor (ON vs. OFF).

Interaction among the three groups was tested by means of one factor analysis of variance (Anova). In the case of

Table 3 – Saccadic parameters in DBS-STN treated patients and pharmacologically treated patients in their ON and OFF status.

Variable	DBS-STN treated patients $n = 20$		p	Pharmacologically treated patients $n = 44$		p
	OFF	ON		OFF	ON	
Visually guided saccades						
Latency [ms]	325.7 (±116.2)	246.3 (±57.3)	<0.01	256.8 (±68.5)	307.2 (±82.7)	<0.01
Amplitude 10°	7.6 (±25)	9.1 (±1.9)	n.s.	8.9 (±2.3)	9.7 (±3.2)	n.s.
Amplitude 20°	12.6 (±4.3)	15.7 (±4.2)	n.s.	15.3 (±4.1)	14.4 (±5.4)	n.s.
Peak velocity 10° [°/s]	224.2 (±66.6)	276.8 (±72.9)	n.s.	303.3 (±105.0)	278.6 (±117.8)	n.s.
Peak velocity 20° [°/s]	262.7 (±81.6)	326.9 (±89.4)	n.s.	360.9 (±118.0)	323.6 (±145.8)	n.s.
Antisaccades						
[*n*]	34%	28%	n.s.	38%	32%	n.s.
Latency [ms]	520.9 (±130.4)	430.5 (±131.2)	n.s.	515.9 (±247.2)	509.9 (±199.5)	n.s.
Peak velocity [°/s]	202.2 (±53.1)	273.4 (±83.6)	n.s.	240.9 (±85.2)	213.5 (±71.9)	n.s.
Memory-guided saccades						
[*n*]	25%	30%	n.s.	22%	22%	n.s.
Latency 10° [ms]	652.1 (±331.1)	455.8 (±139.5)	n.s.	571.0 (±307.5)	487.9 (±212.9)	n.s.
Latency 20° [ms]	521.4 (±225.6)	417.1 (±131.3)	n.s.	566.7 (±215.2)	440.9 (±152.5)	n.s.
Amplitude 10°	8.8 (±2.0)	9.6 (±1.3)	n.s.	10.2 (±3.9)	10.1 (±3.6)	n.s.
Amplitude 20°	16.7 (±1.8)	17.3 (±2.5)	n.s.	16.0 (±5.8)	15.6 (±3.5)	n.s.
Peak velocity 10° [°/s]	199.1 (±45.5)	239.9 (±77.8)	n.s.	241.9 (±125.5)	203.3 (±64.4)	n.s.
Peak velocity 20° [°/s]	215.7 (±95.6)	267.5 (±83.7)	<0.01	288.0 (±130.1)	257.8 (±97.4)	n.s.

Data are presented as mean (±SD).
n.s., not significant.
n, percentage of saccades properly accomplished.

significance of the overall effect post hoc tests were run (Tukey honest difference test). Significance was set at the 0.05 level. SPSS 21 software was used to analyze the data (IBM Corp., 2012).

3. Results

The characteristics of the PD patients are presented in Table 1. DBS-STN patients required a significantly lower L-dopa equivalent daily dose, presented with better motor control in their OFF status measured by MDS-UPDRS part III and had better quality of life as measured by the PDQ-39. Each group of PD patients in the OFF status differed from the controls in almost all parameters of both visually and internally guided saccades (Table 2).

Table 3 summarizes all studied pre- and post-therapeutic saccade parameters. In pharmacologically treated patients all parameters showed tendency to worsen in their ON status (visually guided saccades: delayed, smaller and slower; internally guided saccades: less number of properly accomplished saccades, smaller and slower) as compared to OFF status. Activating DBS-STN showed tendency to improve all studied parameters (visually guided saccades: decreased latency, increased amplitude, increased peak saccadic velocity; internally guided saccades: higher number of properly accomplished saccades, increased amplitude, increased peak saccadic velocity). Comparison of the studied saccade parameters between the ON status of DBS-STN treated patients, ON status of the pharmacologically treated patients and the controls showed that as many as 73% of the studied parameters in the DBS-STN treated patients reached similar values as in the controls, as against 26% in pharmacologically treated patients (Table 4).

4. Discussion

This study comparing the influence of L-dopa and DBS-STN on saccades in advanced PD, showed contrasting results. DBS-STN, as compared to L-dopa improved almost all the studied saccadic parameters; and the results for the majority (73%) of them were similar to those in the controls.

Table 4 – Comparison of saccadic parameter changes between DBS-STN treated patients in their ON status. L-Dopa treated patients in their ON status and in healthy controls.

Variable	Groups		Mean difference	Mean error	*p*
Visually guided saccades					
Latency [ms]	DBS-STN	Controls	.02	.03	.826
	L-Dopa	Controls	.12	.02	<.001
Amplitude 10°	DBS-STN	Controls	−.03	.03	.556
	L-Dopa	Controls	−.05	.02	.026
Amplitude 20°	DBS-STN	Controls	−.06	.03	.143
	L-Dopa	Controls	−.10	.03	<.001
Peak velocity 10° [°/s]	DBS-STN	Controls	−.06	.03	.185
	L-Dopa	Controls	−.06	.03	.033
Peak velocity 20° [°/s]	DBS-STN	Controls	−.07	.03	.098
	L-Dopa	Controls	−.09	.03	.004
Antisaccades					
[%]	DBS-STN	Controls	−.40	.09	<.001
	L-Dopa	Controls	−.41	.07	<.001
Latency [ms]	DBS-STN	Controls	.11	.04	.010
	L-Dopa	Controls	.18	.03	<.001
Peak velocity [°/s]	DBS-STN	Controls	−.02	.04	.805
	L-Dopa	Controls	−.13	.03	<.001
Memory-guided saccades					
[%]	DBS-STN	Controls	−.13	.12	.536
	L-Dopa	Controls	−.42	.10	<.001
Latency 10° [ms]	DBS-STN	Controls	.09	.05	.103
	L-Dopa	Controls	.08	.04	.135
Latency 20° [ms]	DBS-STN	Controls	.06	.04	.313
	L-Dopa	Controls	.05	.04	.454
Amplitude 10°	DBS-STN	Controls	−.06	.03	.095
	L-Dopa	Controls	−.06	.02	.068
Amplitude 20°	DBS-STN	Controls	−.07	.03	.033
	L-Dopa	Controls	−.11	.02	<.001
Peak velocity 10° [°/s]	DBS-STN	Controls	−.08	.04	.095
	L-Dopa	Controls	−.17	.03	<.001
Peak velocity 20° [°/s]	DBS-STN	Controls	−.11	.04	.024
	L-Dopa	Controls	−.17	.04	<.001

[%], percentage of saccades properly accomplished.

Only seven studies investigating the influence of DBS-STN on saccadic eye movements in PD patients have been published [2,3,5,6]. The presented study included a larger group of patients with the advanced PD than in previous research. Furthermore, prior studies accepted concomitant treatment with antiparkinsonian drugs during the procedure [5], the majority applied short "stim off" time (up to 15 min) and had a more limited battery of tests for saccadic characteristics [2]. Unlike the current study, the other studies did not compare the patients' results to those of healthy controls. The effect of DBS-STN can be explained by its impact on the correction of excitability of the cortical areas involved in the saccades generation.

The presented study showed that L-dopa treatment showed a tendency to deteriorate almost all analyzed saccadic parameters. It is difficult to compare our results with previous reports, since in those studies the patients were mostly in their early stage of the disease [7,8,15].

In addition, the prior studies included smaller groups of patients (most included less than 20 cases) [7,8,15], they considered only 3 or less saccadic parameters [4,7,8,15], in two studies both L-dopa and dopaminergic agonists were accepted [8,15], and finally, the same dosage of L-dopa was applied irrespectively of the stage of the disease [7]. It is well known that L-dopa effects of treatment depend on the stage of the disease; it loses its efficacy during long-term therapy. In advanced PD the presence of complications of L-dopa therapy is predominant. It is possible that detrimental effect of L-dopa on saccadic movements is part of late adverse effect profile of this drug.

Limitations of the present study include the fact that the same PD subjects were not assessed in all four intervention states [medication/DBS] (OFF OFF; OFF ON; ON OFF; ON ON) using a standardized dosage of L-dopa. In addition, the order of L-dopa OFF and ON states or STN-OFF and ON states was not randomized. PD patients tend to fatigue easily when participating in series of assessments, and saccade performance in particular may be affected by fatigue. However, for the sake of practicality classical guidelines of patient examination used in numerous other studies were reproduced here [12,13], and, as specified in Methods, PD patients rested between trials to minimize fatigue. Lack of examiner-blinding in the subject-OFF or ON status is another potential limitation. However, the measurement method was highly objective. Finally, the study design was limited to horizontal saccade analysis; however, execution of vertical and horizontal saccades involves a similar final pathway [1].

In conclusion, this study confirmed the saccadic abnormalities in advanced PD and disclosed remarkably conflicting effects of L-dopa and DBS-STN. DBS-STN improved almost all the studied saccadic parameters; and the majority of them reached similar values as those in the controls. Studying the effects of L-dopa and DBS-STN on the ocular motor system may shed more light on the pathogenesis underlying eye movement abnormalities in neurodegenerative disorders. The applied protocol, even if time consuming, can be considered in the clinical setting as a method of a long-term monitoring of DBS-STN effectiveness. Systematic monitoring of saccadic profile in DBS-STN patients can detect the waning of the benefits of DBS-STN in long-term treatment. Further studies are needed.

5. Conclusion

This prospective study comparing the influence of L-dopa and DBS-STN on saccades in advanced PD showed contrasting results between these two treatments; the majority of the studied parameters in patients on DBS-STN were similar as in the controls.

Authors contribution

Małgorzata Dec-Ćwiek: study concept and design, acqusition of data, analysis and interpretation of data, drafting/revision the manuscript; Marcin Tutaj: analysis and interpretation of data, critical revision of the manuscript for important intellectual content; Jean-Michel Gracies: analysis and interpretation of data, critical revision of the manuscript for important intellectual content; Jens Volkmann: analysis and interpretation of data, critical revision of the manuscript for important intellectual content; Monika Rudzińska: study concept and design, acqusition of data, analysis and interpretation of data, study supervision; Agnieszka Słowik: analysis and interpretation of data, drafting/revision the manuscript, critical revision of the manuscript for important intellectual content; Andrzej Szczudlik: analysis and interpretation of data, drafting/revision the manuscript, critical revision of the manuscript for important intellectual content.

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Conflict of interest

Dr Tutaj receives honoraria from Medtronic Poland. The other authors report no disclosures.

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